British Journal of Anaesthesia **98 (1):** 12–18 (2007)
doi:10.1093/bja/ael277 Advance Access publication October 22, 2006

CARDIOVASCULAR

Effects of sevoflurane and propofol on left ventricular diastolic function in patients with pre-existing diastolic dysfunction

M. Filipovic[1]*, I. Michaux[1], J. Wang[1], P. Hunziker[2], K. Skarvan[1] and M. Seeberger[1]

[1]Department of Anaesthesia and [2]Medical Intensive Care Unit, Department of Internal Medicine, University of Basel Hospital, CH-4031 Basel, Switzerland

**Corresponding author. E-mail: mfilipovic@uhbs.ch*

Background. The effects of anaesthetics on left ventricular (LV) diastolic function in patients with pre-existing diastolic dysfunction are not well known. We hypothesized that propofol but not sevoflurane will worsen the pre-existing LV diastolic dysfunction.

Methods. Of 24 randomized patients, 23 fulfilled the predefined echocardiographic criterion for diastolic dysfunction. They received general anaesthesia with sevoflurane 1 MAC (n=12) or propofol 4 μg ml^{-1} (n=11). Echocardiographic examinations were performed at baseline and in anaesthetized patients under spontaneous breathing and under positive pressure ventilation. Analysis focused on peak early diastolic velocity of the mitral annulus (E_a).

Results. During spontaneous breathing, E_a was higher in the sevoflurane than in the propofol group [mean (95% CI) 7.0 (5.9–8.1) *vs* 5.5 (4.7–6.3) cm s^{-1}; P<0.05], reflecting an increase of E_a from baseline only in the sevoflurane group (P<0.01). Haemodynamic findings were similar in both groups, but the end-tidal carbon dioxide content was more elevated in the propofol group (P<0.01). During positive pressure ventilation, E_a was similarly low in the sevoflurane and propofol groups [5.3 (4.2–6.3) and 4.4 (3.6–5.2) cm s^{-1}, respectively].

Conclusions. During spontaneous breathing, early diastolic function improved in the sevoflurane but not in the propofol group. However, during positive pressure ventilation and balanced anaesthesia, there was no evidence of different effects caused by the two anaesthetics.

Br J Anaesth 2007; **98**: 12–18

Keywords: anaesthetics volatile, sevoflurane; anaesthetics i.v., propofol; heart, myocardial function; measurement technique, Doppler echocardiography

Accepted for publication: August 23, 2006

Introduction

Diastolic dysfunction is closely related to reduced exercise tolerance, dyspnoea and increased mortality.[1 2] During diastole, dissociation of calcium from troponin C and active re-uptake of calcium into the sarcoplasmic reticulum are key processes of myosin detachment from actin, causing myocardial relaxation.[3] Many anaesthetics including sevoflurane and propofol alter calcium homeostasis at several subcellular targets, for example the re-uptake of calcium into the sarcoplasmic reticulum.[4–6] These interactions are regarded as the molecular basis for alterations of diastolic and systolic functions caused by anaesthetics. However, little is known about the effects of anaesthetics on diastolic function *in vivo*; current knowledge is mainly based on animal and laboratory studies[7] that show impairment of left ventricular (LV) diastolic function by inhalational anaesthetics[8–10] but no effect on diastolic function by propofol.[11 12] In contrast, our recent study in healthy humans failed to detect any impairment of diastolic function by halothane and sevoflurane but found a slight impairment by propofol.[13]

Given the conflicting findings and the paucity of data in patients, this study was designed to evaluate the effects of sevoflurane and propofol on LV diastolic function in patients with pre-existing diastolic dysfunction but preserved LV systolic function. Pre-existing diastolic dysfunction was assumed in patients with aortic stenosis undergoing aortic valve replacement who had preserved LV systolic function. However, for study inclusion these patients had to fulfil an echocardiographic criterion of LV diastolic dysfunction, that is reduced peak early diastolic velocity of the mitral annulus (E_a).[14 15] Based on our previous findings in

healthy subjects,[13] we hypothesized that sevoflurane would have no negative effect on LV diastolic function whereas we expected propofol to impair early diastolic function, as indicated by a further decrease in E_a. This hypothesis was tested in two experimental conditions, that is anaesthesia with single agent and spontaneous breathing (step I), and balanced anaesthesia and positive pressure ventilation (step II), as commonly performed in clinical practice.

Methods

The institutional Review Board at the University of Basel Hospital approved the study for which patients with valvular aortic stenosis undergoing aortic valve replacement were eligible. Exclusion criteria were more than mild aortic valve regurgitation, ejection fraction <50%, coronary artery or cerebral vascular disease, pulmonary disease under chronic medication, age <18 or >75 yr, or BMI >30 kg m^{-2}. Patients were only included in the study if they fulfilled a previously published echocardiographic criterion of diastolic dysfunction, that is, if peak early diastolic velocity of the septal annulus ($E_{a\ sept}$) was <8.5 cm^{-1}.[14 15] Twenty-four patients were enrolled after obtaining their informed written consent. Patients were randomly assigned to undergo anaesthesia with either sevoflurane or propofol. A computer-generated random list was used.

After arrival in the preoperative area, i.v. access was established and Ringer's lactate administered to replace the fluid deficit caused by overnight fasting. The deficit per hour of fasting was calculated as follows: 4 ml kg^{-1} for the first 10 kg of body weight, 2 ml kg^{-1} for the second 10 kg and 1 ml kg^{-1} for every additional kilogram of weight. Twenty-five per cent of the deficit was replaced before the start of the study, a total of 30% by the end of anaesthesia step I (see below) and a total of 35% by the end of anaesthesia step II (see below). Two-lead electrocardiography, pulse oximetry and invasively measured arterial pressure (PCMS Workstation 90308-15-03, SpaceLabs Inc., Redmond, WA, USA), and the bispectral index (BIS; Aspect 1000, Aspect Medical Systems Inc., Natick, MA, USA; software version 1.01) were monitored continuously. As soon as the patient was anaesthetized, end-tidal concentrations of carbon dioxide and sevoflurane were measured continuously at the tip of the laryngeal mask or orotracheal tube (Caponomac Ultima, Datex, Helsinki, Finland). A decrease in systolic arterial pressure >30% from baseline was defined as clinically relevant hypotension and treated with a single or repeated i.v. bolus of phenylephrine 25 μg.

The first transthoracic echocardiography (TTE) was performed in an awake, unpremedicated patient (baseline data) in a partial left lateral position. The same position was used during all further echocardiographic examinations. Thereafter, anaesthesia was induced by inhalation of sevoflurane (Sevorane®, Abbott International Ltd., Abbott Park, IL, USA) in 100% oxygen or by i.v. infusion of propofol (Diprivan®, Zeneca Pharmaceuticals, Macclesfield, Cheshire, UK) delivered by a target-controlled infusion system (TCI, Diprifusor®, Zeneca Pharmaceuticals). No other narcotics or opioids were used. After placement of a laryngeal mask, the inspiratory oxygen concentration was adjusted to 0.4 and the administration of anaesthetics was reduced to 1 MAC of the inhalational anaesthetic (2% end-tidal concentration of sevoflurane), or to propofol 4 μg ml^{-1}. As soon as anaesthetic and haemodynamic steady-state conditions were reached, a second TTE was performed (step I). At the end of steps I and II, blood was withdrawn from the arterial line in patients of the propofol group for chromatographic analysis of propofol blood concentrations (modified from Plummer and collegues[16]).

After finishing step I, fentanyl 2 μg kg^{-1} and rocuronium 0.6 mg kg^{-1} were administered and the patient's trachea was intubated. Intermittent positive pressure ventilation (IPPV) was performed to achieve normoventilation (end-tidal carbon dioxide content 4.5–5 kPa). A transoesophageal echo probe was then placed in the oesophagus.

As soon as steady-state conditions were reached at 1 MAC of sevoflurane or i.v. propofol 4 μg ml^{-1}, a transoesophageal echocardiography (TOE) was performed (step II). After finishing this examination, each patient underwent aortic valve replacement.

All echocardiograms were obtained with a Sonos 5500 ultrasonographic system (Philips Medical Systems, Best, The Netherlands) according to current guidelines.[17–19] For TTE, a 1.8–2.1/3.6–4.1 MHz S4 probe was used, and for TOE a 4–7 MHz multiplane probe. The echocardiographic data were digitally stored for subsequent off-line analysis. Standard LV short-axis and two- and four-chamber views were obtained by the parasternal and apical views for TTE and by standard midoesophageal and transgastric views for TOE. For recordings of pulsed-wave tissue Doppler

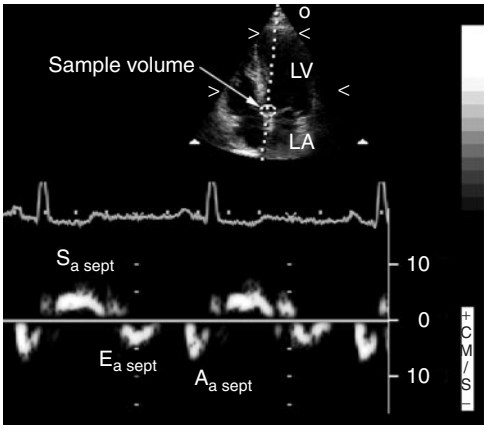

Fig 1 Pulsed-wave Doppler tissue imaging of the septal mitral annulus. The position of the pulsed-wave Doppler sample volume is demonstrated in the two-dimensional echocardiographic transthoracic image of the apical four-chamber view in the upper part of the figure. LA=left atrium; LV=left ventricle; $E_{a\ sept}$=peak early diastolic velocity of septal mitral annulus; $A_{a\ sept}$=peak late diastolic velocity of septal mitral annulus; $S_{a\ sept}$=peak systolic velocity of septal mitral annulus.

imaging, the sample volume was placed at the septal and lateral sides of the mitral annulus and the acoustic power and the filter frequencies of the system set to the lowest possible values (Fig. 1). The main echocardiographic indicator of early diastolic function was predefined as the average of the peak early diastolic peak velocity of septal and the lateral mitral annulus (E_a).[14 15] The comprehensive echocardiographic assessment included measurement of the following variables: peak early (E_a) and late (A_a) diastolic, and peak systolic (S_a) velocities of septal and lateral mitral annuli, peak early (E) and peak late (A) transmitral filling velocities, deceleration time (DT) of E, isovolumic relaxation time (IVRT), and end-diastolic (EDA) and end-systolic (ESA) areas. From these data, the following parameters were calculated: the ratios of E/A and E/E_a and the fractional area change {FAC=[(EDA−ESA)/EDA]×100}. All variables were measured at end-expiration over three preferably consecutive cardiac cycles and averaged by an experienced physician-echocardiographer blinded to all other study data. To determine intra-observer and interobserver variability, a random sample of 25% of the tissue Doppler recordings was submitted twice to the first investigator and once to a second investigator. The variabilities then were calculated as the mean absolute difference between both readings divided by their mean and expressed as a percentage.

Continuous variables are presented as mean and 95% CIs. The Fisher's exact test was used for analyses of dichotomous variables. Continuous variables were compared by using non-parametric tests: the Mann–Whitney test was used for comparisons between the two study groups at the different steps of the study. The Wilcoxon test was used for comparison of the findings at baseline *vs* anaesthesia step I within one study group. Comparisons during step II were only performed between the study groups because of the different echocardiographic techniques used at step I (TTE) and step II (TOE). $P<0.05$ was considered statistically significant. All statistical analyses were performed using a SPSS for Windows 11.5 computer package (SPSS Inc., Chicago, IL, USA). The sample size calculation was based on our previous study[13] estimating that 12 patients per group would allow for detection of a 25% difference in E_a with a power of 80% for intragroup comparison and of a 33% difference in E_a for intergroup comparisons.

Results

One patient in the propofol group had E_a >8.5 cm s^{-1} and was excluded from analysis, thus leaving 11 patients in the propofol and 12 patients in the sevoflurane group. Both groups had similar patients' characteristics (Table 1) and similar baseline findings (Table 2 and Appendix).

From baseline to anaesthesia step I, E_a increased in the sevoflurane group ($P<0.01$) but remained unchanged in the propofol group. This resulted in a higher E_a in the sevoflurane group than in the propofol group ($P<0.05$; Table 2 and Fig. 2). Accordingly, the E_a/A_a ratio was higher in the

Table 1 Patient characteristics. Values are mean (95% CI) or numbers. There were no differences between the groups. ACE, angiotensin converting enzyme

	Sevoflurane (n=12)	Propofol (n=11)
Women	4	4
Age (yr)	61 (52–69)	63 (58–69)
Weight (kg)	71 (64–79)	75 (68–82)
Height (cm)	168 (163–172)	167 (162–173)
BMI (kg m^{-2})	25 (23–28)	27 (25–29)
Haemoglobin (g litre^{-1})	142 (131–154)	147 (137–156)
Creatinine (μmol litre^{-1})	69 (57–80)	76 (69–83)
Chronic medication		
β-receptor blockers	1	3
ACE inhibitors	2	1
Diuretics	2	2

Table 2 Pulsed-wave tissue Doppler findings at baseline and during anaesthesia with sevoflurane 1 MAC, or propofol 4 μg ml^{-1} under spontaneous ventilation (step I). Values are mean (95% CI). There were no differences between the groups in baseline findings. *$P<0.05$ baseline *vs* step I (within-group comparison). §$P<0.05$ sevoflurane *vs* propofol (between-group comparison). E_a, peak early diastolic velocity of the mitral annulus; A_a, peak late diastolic velocity of the mitral annulus; S_a, peak systolic velocity of the mitral annulus

	Sevoflurane		Propofol	
	Baseline	Anaesthetized spontaneous breathing	Baseline	Anaesthetized spontaneous breathing
E_a (cm s^{-1})	6.2 (5.3–7.1)	7.0 (5.9–8.1)*	5.5 (4.4–6.6)	5.5 (4.7–6.3)§
A_a (cm s^{-1})	10.3 (9.0–11.5)	7.7 (6.7–8.7)*	9.0 (7.6–10.4)	8.6 (7.8–9.3)
E_a/A_a	0.6 (0.5–0.8)	1.0 (0.8–1.2)*	0.6 (0.5–0.8)	0.7 (0.5–0.8)§
S_a (cm s^{-1})	7.1 (6.5–7.6)	5.9 (5.4–6.5)*	6.5 (5.8–7.3)	6.5 (5.7–7.3)

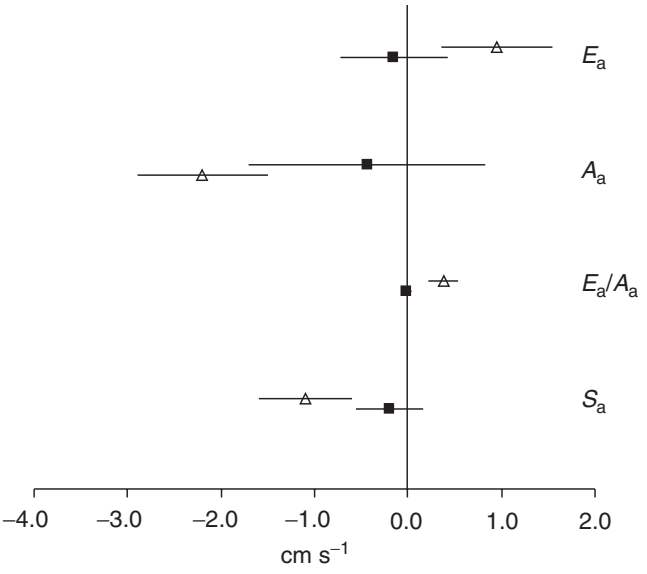

Fig 2 Mean changes and 95% CIs of tissue Doppler derived variables of the mitral annulus from baseline to anaesthesia with 1 MAC sevoflurane (open triangle) or 4 μg ml^{-1} propofol (filled square) under spontaneous breathing (step I). E_a=peak early diastolic velocity of the mitral annulus; A_a=peak late diastolic velocity of the mitral annulus; S_a=peak systolic velocity of the mitral annulus.

sevoflurane than in the propofol group, whereas there was no difference in A_a or S_a between the groups. In the sevoflurane group, the mitral inflow patterns changed (evident as a decrease in *A* and an increase in the *E*/*A* ratio) and the IVRT tended to decrease. In the propofol group, all these variables remained unchanged. However, there were no significant differences between the groups. The haemodynamic variables and the E/E_a ratio were similar in both study groups, as were the number (4 *vs* 6) and dosage (2.4 *vs* 1.9 $\mu g\ kg^{-1}$) of phenylephrine administered, and the BIS values. However, end-tidal carbon dioxide was lower in the sevoflurane than in the propofol group [mean (95% CI) 6.2 (5.7–6.8) kPa and 7.1 (6.7–7.5) respectively; $P<0.01$]. These data are shown in detail in the Appendix.

During anaesthesia and IPPV, there was no difference in E_a between the study groups, and A_a and S_a were also similar (Table 3). However, the E_a/A_a ratio was higher in the sevoflurane group. The haemodynamic findings, the E/E_a ratio, the mitral inflow patterns, the number (9 *vs* 8) and the dosage (5.3 *vs* 6.2 $\mu g\ kg^{-1}$) of administered phenylephrine, end-tidal carbon dioxide and the BIS values were similar in both groups (Appendix).

The intra-observer variability for E_a was 4.3% (2.2–5.9) for data obtained by TTE and 3.0% (0–6.2) for data obtained by TOE. The corresponding values for the interobserver variability were 4.8% (2.5–7.1; TTE) and 4.3% (0–9.2; TOE).

Discussion

This study investigated the effects of sevoflurane and propofol on LV diastolic function in patients with pre-existing diastolic dysfunction but preserved systolic function. During spontaneous breathing and consecutive elevation of end-tidal carbon dioxide, sevoflurane slightly improved early diastolic function whereas propofol had no detectable effect. In contrast, IPPV and normal end-tidal carbon dioxide the early diastolic function in both the groups was similarly impaired.

This study used two experimental settings to test the effects of sevoflurane and propofol on diastolic function. The first setting (spontaneous breathing) allowed for performing anaesthesia solely with the one anaesthetic and to avoid the effect of IPPV on venous pooling, preload and afterload. However, spontaneous breathing resulted in an inevitable elevation of end-tidal carbon dioxide and, moreover, it does not represent common clinical practice. In contrast, the second setting (balanced anaesthesia and IPPV), maintains normocapnia. It is unknown whether the observed changes were caused only by the drug under primary investigation or were also influenced by opioids, neuromuscular blocking drugs, muscular paralysis and/or the consequences of IPPV.

Table 3 Pulsed-wave tissue Doppler findings during anaesthesia with sevoflurane 1 MAC, or propofol 4 $\mu g\ ml^{-1}$ and IPPV (step II). Values are mean (95% CI). §$P<0.05$ sevoflurane *vs* propofol, (between-group comparison). E_a, peak early diastolic velocity of the mitral annulus; A_a, peak late diastolic velocity of the mitral annulus; S_a, peak systolic velocity of the mitral annulus

	Sevoflurane	Propofol
E_a (cm s^{-1})	5.3 (4.2–6.3)	4.4 (3.6–5.2)
A_a (cm s^{-1})	4.1 (3.4–4.7)	5.3 (4.4–6.3)
E_a/A_a	1.4 (0.9–1.9)	0.9 (0.6–1.1)§
S_a (cm s^{-1})	4.6 (3.9–5.3)	4.7 (3.8–5.6)

The present finding that sevoflurane alone had a favourable effect on diastolic function in patients with pre-existing diastolic dysfunction is in agreement with our previous finding in healthy subjects.[13] These findings in man conflict with most animal and *in vitro* studies reporting marked changes in myocardial relaxation and diastolic filling induced by inhalational anaesthetics.[8–10 20] These previous findings were explained by the interference of inhalational anaesthetics with calcium re-uptake from the cytosol into the sarcoplasmatic reticulum during diastole,[5] a key mechanism of myocardial relaxation.[3] However, there are important differences between our study and previous studies that might explain the conflicting results. Most importantly, the previous studies investigated healthy animals[9 10 20] or isolated hearts from healthy animals,[8] and some studies used higher doses of inhalational anaesthetics[8] or administered additional drugs for induction of anaesthesia.[9] In contrast, our study evaluated patients with pre-existing impairment of diastolic function, used the clinical dose of anaesthetics, did not use drugs other than that under investigation for induction of anaesthesia (step I) and assessed diastolic function non-invasively by Doppler echocardiography according to current cardiological guidelines.[17 18]

A finding consistent with previous studies[20] was that sevoflurane impaired systolic atrial and ventricular functions, as indicated by decreases of S_a and A_a. In contrast, these variables were unchanged during propofol anaesthesia, indicating no effect of propofol on systolic function.

The present result that propofol alone had no unfavourable effect on diastolic function in patients with pre-existing diastolic dysfunction is in agreement with most previous animal[11 12] and human[21] studies. A recently published study found no effect of low-dose propofol on echocardiographic parameters of diastolic function during conscious sedation of patients with pre-existing diastolic dysfunction.[21]

Only three studies reported impairment of diastolic function by propofol.[13 22 23] As with sevoflurane, such an effect on diastolic function can be explained by intracellular effects of the anaesthetic: propofol impairs re-uptake of calcium by the sarcoplasmatic reticulum[6 24] and modulates phosphorylation of the contractile muscles,[25] which are the mechanisms directly involved in myocardial muscle relaxation. In rabbits with cardiac hypertrophy, there was impairment of diastolic function by propofol but only at supraclinical doses,[22] while in a dog model of dilated cardiomyopathy there was impairment of early diastolic LV filling.[23]

In our previous study, we found mild impairment of diastolic function by propofol in spontaneously breathing healthy young subjects, which was based on a slight

decrease in E_a and an increase in heart-rate corrected IVRT.[13] We considered this observed impairment of diastolic function by propofol to be too small to be the cause of clinical concern.[13] Similarly, the present results also do not support the clinical importance of the intracellular effects of propofol, although we again found a prolonged IVRT in the propofol group during spontaneous breathing. The predefined outcome variable, the tissue Doppler imaging indicator E_a, did not change during propofol anaesthesia in spontaneously breathing patients. Although IVRT is one of the traditional echocardiographic indicators of diastolic function,[18] we did not focus on this in this study because E_a has three important advantages: Its main advantage in patients with pre-existing diastolic function is that E_a has a unimodal distribution[14 15] with a gradual decrease in going from mild to severe diastolic dysfunction.[26] This characteristic implies that an increase in E_a indicates improvement, while a decrease in E_a reflects impairment of diastolic function. In contrast, changes in IVRT (and similarly in the transmitral *E/A* ratio) are U-shaped during transition from normal diastolic function to severe diastolic dysfunction.[14] In patients with pre-existing diastolic dysfunction, as studied here, this characteristic implies that an increase in IVRT (or in the *E/A* ratio) is equivocal and can indicate either improvement or deterioration. A second advantage of E_a is that it is less load-dependent than IVRT,[26] while the third advantage of E_a is that it closely correlates with the time constant of the decrease in LV pressure τ,[15 27] the invasive gold standard of evaluation of LV relaxation. In cardiac patients, E_a has been widely used to define the presence and severity of diastolic dysfunction.[2 14 15 17]

As expected during spontaneous breathing in anaesthetized patients, end-tidal carbon dioxide was elevated in both study groups, the elevation being more pronounced in the propofol group. To what extent these changes altered the myocardial calcium homoeostasis, as shown *in vitro* using a high carbon dioxide load,[28] those altering the effects of the anaesthetic agents cannot be determined from our clinical investigation.

There were no differences in E_a between the sevoflurane and the propofol group during balanced anaesthesia, IPPV and normocapnia. This result agrees with our previous study in healthy subjects during balanced anaesthesia with sevoflurane and propofol that also found no difference in E_a during IPPV.[13] However, in both study groups early diastolic function remained impaired, as indicated by the low E_a values.

Potential reasons for the different findings during single-agent anaesthesia and spontaneous breathing *vs* balanced anaesthesia and IPPV cannot be differentiated by the experimental design used. Reasons may include different concentrations of carbon dioxide, the addition of opioids and neuromuscular blocking drugs, muscular paralysis and/or the consequences of IPPV. The haemodynamic effect of opioids such as fentanyl might depend on concomitant drug administration.[29] Because TTE often does not allow for optimal image quality during IPPV, we used TOE during this study step. However, the difference in echocardiographic technique between TTE and TOE makes direct comparison of the findings questionable, and we did not perform statistical comparisons of the TTE and TOE derived findings.

This study has some limitations. First, the results derived from patients of this study cannot necessarily be extrapolated to patients with other than isolated non-ischaemic diastolic dysfunction. The second limitation of this study is that the equipotency of propofol and sevoflurane can be questioned. However, the similar BIS values in both groups and the comparable haemodynamics indicated a similar 'depth' of anaesthesia and, accordingly, equipotency. Thirdly, invasively derived information on the decrease in LV isovolumic pressure or its time constant τ was not available. However, E_a is a well-validated echocardiographic parameter of diastolic function[14 15] and closely correlates with τ.[15 27] E_a is widely used in TTE and its feasibility by TOE has been recently demonstrated.[13 30] In addition, the E/E_a ratio, an echocardiographic parameter of LV filling pressure,[31] did not change throughout the study. Finally, one might speculate that the low E_a values during IPPV were caused by clinically undetected myocardial ischaemia.[32] However, there was no electrocardiographic or echocardiographic evidence of ischaemia in any of the study patients. Furthermore, patient selection was designed to minimize the risk of confounding ischaemia, as only patients free from angiographic signs of coronary artery disease were eligible.

Patients with diastolic dysfunction have an increased cardiac morbidity and mortality[2 3] and diastolic dysfunction may contribute to perioperative congestive heart failure. The present results indicated that, when given alone, sevoflurane slightly ameliorates early diastolic function in spontaneously breathing patients with pre-existing diastolic dysfunction and that propofol had no effect. During IPPV and balanced anaesthesia, diastolic function remained impaired in the sevoflurane and propofol groups with no differences between the study groups. The present findings demonstrated ongoing impairment of diastolic function under balanced anaesthesia but did not favour sevoflurane or propofol as an agent that would be advantageous in patients with pre-existing diastolic dysfunction. An outcome study is required to confirm these results.

Acknowledgements

The authors thank R. N. Claudia Werner and R. N. Esther Seeberger, Department of Anaesthesia, University Hospital Basel, Basel, Switzerland, for help in data acquisition, and Joan Etlinger, BA, Department of Anaesthesia, University Hospital Basel, Basel, Switzerland, for editorial assistance. This study was funded by the Swiss National Science Foundation (grant no. 3200-059817), Bern, Switzerland; the International Anaesthesia Research Society, Cleveland, OH, USA.

Appendix

Table A1 Haemodynamic and echocardiographic findings at baseline and during anaesthesia with sevoflurane 1 MAC or propofol 4 μg ml^{-1} under spontaneous ventilation (step I) and under IPPV (step II). Values are mean (95% CI). *P<0.05 baseline *vs* step I (within group comparison), §P<0.05 sevoflurane *vs* propofol. There were no sevoflurane *vs* propofol differences at baseline findings and there were no sevoflurane *vs* propofol differences at step II. MAC, minimum alveolar concentration; IPPV, intermittent positive pressure ventilation; E, peak early transmitral filling velocity; A, peak late transmitral filling velocity; DT, deceleration time of E; E_a, peak early diastolic velocity of the mitral annulus; IVRT, isovolumetric relaxation time; EDA, end-diastolic area; ESA, end-systolic area; FAC, fractional area change; MAP, mean arterial pressure; HR, heart rate

	Sevoflurane			**Propofol**		
	Baseline	**Step I Spontaneous breathing**	**Step II IPPV**	**Baseline**	**Step I Spontaneous breathing**	**Step II IPPV**
E (cm s^{-1})	63 (53–73)	69 (59–79)	57 (48–67)	65 (58–73)	57 (47–68)	53 (45–61)
A (cm s^{-1})	82 (71–92)	58 (47–68)*	38 (31–44)	75 (57–93)	72 (58–85)	47 (35–59)
E/A	0.8 (0.6–0.9)	1.3 (1.0–1.6)*	1.7 (1.2–2.1)	1.0 (0.7–1.3)	0.8 (0.6–1.0)	1.3 (0.8–1.8)
DT (ms)	280 (220–340)	229 (198–261)*	253 (211–295)	257 (209–305)	283 (214–351)	328 (255–400)
E/E_a	10.5 (8.5–12.4)	10.1 (7.8–12.5)	11.0 (8.9–13.1)	12.5 (10.5–14.6)	11.0 (9.0–13.1)	12.7 (10.6–14.9)
IVRT (ms)	87 (71–103)	78 (62–93)	105 (79–131)	93 (78–109)	114 (85–143)	131 (108–154)
EDA (cm^2)	16.2 (14.7–17.7)	15.3 (13.3–17.3)	12.9 (10.7–15.0)	16.4 (14.3–18.5)	14.1 (12.1–16.1)*	13.2 (11.3–15.1)
ESA (cm^2)	4.9 (3.4–6.4)	4.7 (3.5–5.9)	3.4 (2.5–4.3)	5.6 (3.6–7.6)	4.6 (2.9–6.2)*	4.1 (2.1–6.1)
FAC (%)	70 (62–78)	69 (61–78)	74 (67–81)	67 (63–75)	69 (61–80)	70 (61–80)
MAP (mm Hg)	95 (87–103)	70 (66–74)*	65 (61–68)	98 (89–107)	66 (61–72)*	66 (61–71)
HR (beats min^{-1})	63 (56–71)	62 (55–68)	56 (50–62)	61 (56–65)	65 (57–72)	53 (50–57)
E'_{CO_2} (kPa)		6.2 (5.7–6.8)§	4.7 (4.6–4.9)		7.1 (6.7–7.5)	4.7 (4.5–4.8)
Anaesthetic ($\%_{et}$; μg ml^{-1}_{blood})		2.0 (2.0–2.0)	2.0 (1.9–2.0)		6.5 (5.5–7.5)	6.8 (5.7–7.8)
BIS	94 (92–97)	41 (34–57)*	37 (32–42)	94 (93–96)	39 (34–43)*	36 (32–41)

References

1 Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. *Circulation* 2002; **105**: 1387–93

2 Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003; **289**: 194–202

3 Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part II: causal mechanisms and treatment. *Circulation* 2002; **105**: 1503–8

4 Pagel PS, Grossman W, Haering JM, Warltier DC. Left ventricular diastolic function in the normal and diseased heart. Perspectives for the anesthesiologist (1). *Anesthesiology* 1993; **79**: 836–54

5 Lee DL, Woodruff AC. Mechanisms of myocardial depression by volatile anaesthetics. *Anaesth Pharmacol Physiol Rev* 1996; **4**: 74–87

6 Riou B, Besse S, Lecarpentier Y, Viars P. *In vitro* effects of propofol on rat myocardium. *Anesthesiology* 1992; **76**: 609–16

7 Hanley PJ, Ter Keurs HE, Cannell MB. Excitation-contraction coupling in the heart and the negative inotropic action of volatile anesthetics. *Anesthesiology* 2004; **101**: 999–1014

8 Skeehan TM, Schuler HG, Riley JL. Comparison of the alteration of cardiac function by sevoflurane, isoflurane, and halothane in the isolated working rat heart. *J Cardiothorac Vasc Anesth* 1995; **9**: 706–12

9 Humphrey LS, Stinson DC, Humphrey MJ, *et al.* Volatile anesthetic effects on left ventricular relaxation in swine. *Anesthesiology* 1990; **73**: 731–8

10 Graham MR, Thiessen DB, Mutch WA. Isoflurane and halothane impair both systolic and diastolic function in the newborn pig. *Can J Anaesth* 1996; **43**: 495–502

11 Graham MR, Thiessen DB, Mutch WA. Left ventricular systolic and diastolic function is unaltered during propofol infusion in newborn swine. *Anesth Analg* 1998; **86**: 717–23

12 Pagel PS, Schmeling WT, Kampine JP, Warltier DC. Alteration of canine left ventricular diastolic function by intravenous anesthetics *in vivo*. Ketamine and propofol. *Anesthesiology* 1992; **76**: 419–25

13 Filipovic M, Wang J, Michaux I, Hunziker P, Skarvan K, Seeberger MD. Effects of halothane, sevoflurane and propofol on left ventricular diastolic function in humans during spontaneous and mechanical ventilation. *Br J Anaesth* 2005; **94**: 186–92

14 Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. *J Am Coll Cardiol* 1998; **32**: 865–75

15 Sohn DW, Chai IH, Lee DJ, *et al.* Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol* 1997; **30**: 474–80

16 Plummer GF. Improved method for the determination of propofol in blood by high-performance liquid chromatography with fluorescence detection. *J Chromatogr* 1987; **421**: 171–6

17 Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002; **15**: 167–84

18 Rakowski H, Appleton C, Chan KL, *et al.* Canadian consensus recommendations for the measurement and reporting of diastolic dysfunction by echocardiography: from the Investigators of Consensus on Diastolic Dysfunction by Echocardiography. *J Am Soc Echocardiogr* 1996; **9**: 736–60

19 Schiller NB, Shah PM, Crawford M, *et al.* Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989; **2**: 358–67

20 Harkin CP, Pagel PS, Kersten JR, Hettrick DA, Warltier DC. Direct negative inotropic and lusitropic effects of sevoflurane. *Anesthesiology* 1994; **81**: 156–67

21 Gare M, Parail A, Milosavljevic D, Kersten JR, Warltier DC, Pagel PS. Conscious sedation with midazolam or propofol does not alter left ventricular diastolic performance in patients with preexisting diastolic dysfunction: a transmitral and tissue Doppler transthoracic echocardiography study. *Anesth Analg* 2001; **93**: 865–71

22 Ouattara A, Langeron O, Souktani R, Mouren S, Coriat P, Riou B. Myocardial and coronary effects of propofol in rabbits with compensated cardiac hypertrophy. *Anesthesiology* 2001; **95**: 699–707

23 Pagel PS, Hettrick DA, Kersten JR, Lowe D, Warltier DC. Cardiovascular effects of propofol in dogs with dilated cardiomyopathy. *Anesthesiology* 1998; **88**: 180–9

24 Sprung J, Ogletree-Hughes ML, McConnell BK, Zakhary DR, Smolsky SM, Moravec CS. The effects of propofol on the contractility of failing and nonfailing human heart muscles. *Anesth Analg* 2001; **93**: 550–9

25 Kanaya N, Gable B, Murray PA, Damron DS. Propofol increases phosphorylation of troponin I and myosin light chain 2 via protein kinase C activation in cardiomyocytes. *Anesthesiology* 2003; **98**: 1363–71

26 Farias CA, Rodriguez L, Garcia MJ, Sun JP, Klein AL, Thomas JD. Assessment of diastolic function by tissue Doppler echocardiography: comparison with standard transmitral and pulmonary venous flow. *J Am Soc Echocardiogr* 1999; **12**: 609–17

27 Nagueh SF, Sun H, Kopelen HA, Middleton KJ, Khoury DS. Hemodynamic determinants of the mitral annulus diastolic velocities by tissue Doppler. *J Am Coll Cardiol* 2001; **37**: 278–85

28 Gambassi G, Hansford RG, Sollott SJ, Hogue BA, Lakatta EG, Capogrossi MC. Effects of acidosis on resting cytosolic and mitochondrial Ca^{2+} in mammalian myocardium. *J Gen Physiol* 1993; **102**: 575–97

29 Tomicheck RC, Rosow CE, Philbin DM, Moss J, Teplick RS, Schneider RC. Diazepam-fentanyl interaction—hemodynamic and hormonal effects in coronary artery surgery. *Anesth Analg* 1983; **62**: 881–4

30 Lobato EB, Willert JL, Looke TD, Thomas J, Urdaneta F. Effects of milrinone versus epinephrine on left ventricular relaxation after cardiopulmonary bypass following myocardial revascularization: assessment by color m-mode and tissue Doppler. *J Cardiothorac Vasc Anesth* 2005; **19**: 334–9

31 Ommen SR, Nishimura RA, Appleton CP, *et al.* Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. *Circulation* 2000; **102**: 1788–94

32 Duval-Moulin AM, Dupouy P, Brun P, *et al.* Alteration of left ventricular diastolic function during coronary angioplasty-induced ischemia: a color M-mode Doppler study. *J Am Coll Cardiol* 1997; **29**: 1246–55